AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

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IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

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FELINE LEUKEMIA VIRUS: AN OVERVIEW

The feline leukemia virus (FeLV) is the etiologic agent of the most important fatal infectious disease complex affecting American cats. FeLV is a horizontally transmitted and vertically transmitted retrovirus. The in vivo host spectrum appears to be restricted to members of the family Felidae and includes domestic breeds as well as certain small exotic cats. Sophisticated molecular studies have demonstrated relationships between FeLV and some retroviruses of rodents; these and other data suggest that an ancient rodent virus may have been transferred in some manner to an ancestor of the domestic cat millions of years ago, and, from this progenitor, FeLV evolved.

Excretion of FeLV occurs primarily in salivary secretions. Virus may also be present in respiratory secretions, feces, urine, and milk. The social grooming habits of cats (licking and biting), sneezing, and the common urban practice of providing shared litter pans and feeding bowls for pet cats are probably the major means by which FeLV is spread. In addition, the exposure of kittens to the virus may be effected by an infected queen or by close contact with other carrier cats: in utero transfer of virus across the placenta and excretion of FeLV in colostrum are both known to occur. Prolonged close contact (days to weeks) probably is required for effective transmission of FeLV. Virus can also be transmitted in blood transfusions from viremic cats and possibly also by the bites of hematophagous arthropods, such as fleas. The time period between initial exposure to an infective dose of FeLV and the development of either persistent viremia or immunity is quite variable and may be dependent in part on the route of virus transmission.

Through recent studies, some of the early steps in the interactions of host tissue and virus during FeLV infection have been identified. Following infection of the lymphoid tissues surrounding the site of initial virus penetration, a low-grade (transient) viremia occurs involving small numbers of mononuclear leukocytes. Virus is transported to other regions of the body, especially to systemic lymphoid tissues, the intestinal tract, and the bone marrow--all areas containing populations of rapidly dividing cells where FeLV replication can be enhanced. This occurs within 2 weeks of the initial viral exposure. Infections of both polymorphonuclear leukocyte and platelet precursor cells in the bone marrow and the subsequent release of infected cells into the circulation result in a second, more profound (persistent) viremia.

In those cats which resist the widespread replication and dissemination of FeLV, virus containment occurs in the early lymphoid stage of infection following transient viremia. In those animals destined to be viremic persistently, infection proceeds and extensive involvement of the bone marrow, pharynx, esophagus, stomach, bladder, respiratory tract, and salivary glands occurs. All cats with persistent viremia are excretors of infectious FeLV and probably remain excretors for the rest of their lives. They then serve as the primary reservoirs of infectious viruses and can transmit infection to healthy, uninfected, susceptible cats with which they come into contact.

The age of the host at the time of infection and the amount and strain of the infective dose of virus transmitted are important determinants of the outcome of any FeLV challenge. Whereas most kittens exposed to FeLV develop persistent viremia, most cats over 6 months of

age resist persistent viremia, suggesting that age-related maturational changes in the immune system are involved. Evidence indicates that the pertinent maturational changes occur in cats between 2 and 4 months of age. However, some older animals may develop persistent viremia if the duration of exposure to FeLV is very long (years).

Cats with persistent viremia can develop a number of disease entities that are either directly or indirectly caused by FeLV. Among the conditions directly caused by FeLV are lymphoid malignancies (lymphosarcoma, lymphocytic leukemia), a number of myeloproliferative disorders, several types of anemia, panleukopenia-like and thymic atrophy syndromes, glomerulonephritis, certain reproductive disorders, and several other conditions. Diseases indirectly caused by FeLV include myriad conditions that can develop secondary to FeLV-induced immunosuppression. The prognosis for survival of cats with persistent infections is exceedingly poor: approximately 50% die within 6 months of infection and over 80% die within 3 years of infection.

Suppression of the normal protective immunologic responses is unquestionably one of the most important consequences of persistent FeLV infection and is especially pertinent to researchers studying AIDS. Both the humoral and cellular arms of the immune system are affected by the virus. A major cause of FeLV-induced immunosuppression appears to be a specific structural protein, p15(E), that is associated with the viral envelope. Both intact and disrupted virus particles retain immunosuppressive capabilities. An array of secondary disease entities is associated with persistent FeLV infection. It has been estimated that nearly 50% of all cats with severe bacterial infections or hemobartonellosis and 75% of cats with toxoplasmosis have an underlying FeLV infection. In addition, FeLV-induced immunosuppression has been associated with chronic stomatitis and gingivitis, poorly healing or recurrent abscesses, pyoderma, chronic respiratory infections, acute colitis, severe otitis, and feline infectious peritonitis (a lethal, systemic coronavirus disease of both domestic and exotic cats). FeLV-induced immunosuppression probably contributes also to the development of FeLV-induced malignancies.

Research into the development of a safe, protective FeLV vaccine has progressed slowly over the past several years, despite increases in our understanding of the biological behavior of FeLV and the pathogenesis of FeLV infection. Several strategies for FeLV immunization have been investigated, including use of inactivated virus vaccines, tumor cell vaccines, envelope glycoprotein vaccines, and live virus vaccines. Recently, a soluble tumor-cell antigen vaccine (STAV) has been developed by a research team headed by Dr. Richard Olsen, College of Veterinary Medicine, Ohio State University. This vaccine contains neither tumor cells nor FeLV; it is a subunit vaccine composed of immunogenically important antigens naturally released from FeLV-induced lymphosarcoma cells grown in vitro. Studies have shown that adult cats as well as kittens vaccinated with STAV produce protective antiviral and antitumor antibodies and that most are protected against the development of FeLV-induced lymphoid malignancies. In addition, although STAV contains the p15(E) protein, its immunosuppressive action is apparently not exerted in vaccinated animals. Further work is currently in progress to evaluate this highly promising form of immunization.

Local control of FeLV has been achieved through the removal of carrier cats with persistent viremia from multiple-cat households in which they are living. The FeLV test-and-removal program uses an immunofluorescence assay (IFA) for detecting FeLV antigen in infected leukocytes and platelets. In a survey of 45 households from which 159 cats with persistent viremia were removed, 99.5% of the FeLV-negative cats not removed (561/564) remained negative on retesting. Multiple-cat households in which FeLV test-and-removal has not been implemented may experience infection rates over 40 times greater than the rates experienced by households in which the program has been successfully introduced. This program and the IFA procedure it employs were developed by a team of researchers headed by Dr. William D. Hardy, Jr. of the Memorial Sloan-Kettering Cancer Center.

The public health significance of FeLV including, most importantly, the qu[illegible]n of the oncogenic potential of FeL[illegible]mans is still largely unknown [illegible]s which were designed to determi[illegible]evalent circulating FeLV and/or ant[illegible] FeLV are in human sera have prod[illegible]conflicting results over the years. Most surveys have failed to find evidence of FeLV infection in humans, even in individuals with lymphoid or other malignancies. However, most cats with FeLV-induced malignancies similarly have little or no circulating virus-neutralizing antibody, and 10-50% are FeLV negative. Until a more complete understanding of the public health implications of FeLV is obtained, the author considers it prudent to restrict as much as possible human exposure to carrier cats with persistent viremia. It must be emphasized, however, that, as of this writing, there is no conclusive evidence that any human illness (including cancer) has ever been caused by FeLV.

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AIDS-RELATED COMPLEX: A DEFINITION

The National Cancer Institute/National Institute of Allergy and Infectious Diseases Extramural AIDS Working Group consists of a sizable number of investigators who receive funding from the National Institutes of Health specifically for AIDS research. Members of the Group see a large number of patients with AIDS and with AIDS-related conditions. In the summer of 1983, selected members of the Group formulated criteria to describe the "Lymphadenopathy Syndrome" or "AIDS Prodrome." Participants in this exercise were Drs. D. Abrams (UCSF), E. Hersh (MD Anderson), J. Allen (CDC), D. Armstrong (Memorial Sloan-Kettering), A. Friedman-Kien (NYU), M. Gottlieb (UCLA), G. Copley (NCI), J. Killen (NCI), and R. Edelman (NIAID). A considerable amount of time was devoted to finding a name for the syndrome. All agreed that the name chosen should not imply a prodromal condition to overt AIDS, considering both the limits of our current level of understanding of the disease and the variety of psychosocial and medical/financial risks which such a name would impose on the patient. The compromise term, AIDS-related complex (ARC), was finally adopted by consensus and used in Group discussions.

In establishing a definition of ARC, the Group used an approach similar to that used by the American Rheumatism Association for developing a standard diagnosis for rheumatoid arthritis. The

diagnosis of ARC depends upon the finding of any two clinical plus any two laboratory abnormalities in a patient with no underlying infectious cause who is in a high risk group for AIDS.

Clinical Signs/Symptoms (minimum duration 3 months): (1) Fever: >100°F, intermittent or continuous, no infectious cause. (2) Weight loss: unexplained, >10% or ≥15 lbs. (3) Lymphadenopathy: ≥2 extrainguinal areas. (4) Diarrhea: intermittent or continuous, no other cause. (5) Fatigue: unexplained and causing decreased physical or mental function. (6) Night sweats: intermittent or continuous, no infectious cause.

Laboratory Abnormalities: (1) Leukopenia, or thrombocytopenia, or anemia, or absolute lymphopenia. (2) Depressed helper:suppressor T cell ratio (≥2 SD). (3) Depressed absolute number of T helper cells (≥2 SD). (4) Depressed blastogenesis (pokeweed and phytohemagglutinin). (5) Elevated serum globulins. (6) Cutaneous anergy.

This definition encompasses the entire ARC syndrome, because enough information was not available at the time to further stratify ARC into logical clinical subcategories. This definition and minimum data set are subject to change based upon new findings. Indeed, both the discovery of a role for HTLV-III in AIDS and the additional insight which has been gained recently concerning the natural history of ARC and its many clinical expressions have forced us, only 9 months after the definition was first formulated, to reconsider the name and the definition. The results of this second consensus effort, just undertaken by the Group, will be published as soon as possible, assuming that a consensus can be reached.

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THYMOPENTIN TREATMENT IN AIDS AND AIDS-RELATED COMPLEX

Many immunomodulators are currently under investigation in AIDS patients. Thymopentin (TP5) is a synthetic pentapeptide. It has been used successfully in the treatment of various congenital immunodeficiency disorders (Aiuti F, Fiorilli M, Quinti I: Lancet, 1983, 1: 551). Its biological activity is similar to that of thymopoietin which induces the maturation of thymocytes and affects the regulation of the immune system (Goldstein G, Scheid MP, Boyse EA et al: Science, 1979, 204:1309-1310). A recent report showed that levels of serum thymic factor were lowered in patients with AIDS (Dardenne M, Bach JF, Safai B: N Engl J Med., 1983, 309:48). We therefore decided to evaluate whether thymopentin could improve the clinical status and alter immunologic parameters of patients with AIDS (Clumeck N, Sonnet J, Taelman H: N Engl J Med., 1984, 310: 492-497) or with the prodrome of AIDS, AIDS-related complex (ARC). This report describes the results of a study of African patients, five with full-blown AIDS and 11 with ARC. ARC was characterized by generalized lymphadenopathy (100% of cases), weight loss (90%), chronic diarrhea (82%), fever (73%), and T cell ratios (OKT4:OKT8) less than 0.5 (91%; mean ratio = 0.20).

The five patients with AIDS received 50 mg TP5 three times a week for 1 month by slow intravenous (IV) infusion (Group A). Six patients with ARC received 50 mg TP5 three times a week by IV bolus for 1 month followed by 50 mg TP5 by slow IV infusion for an additional month (Group

B). The other five ARC patients received 15 mg TP5 three times a week subcutaneously for 1 month (Group C). Various immunological tests were performed on all patients before, during, and after therapy. These included in vitro studies of T cell functions, studies of the blastogenic responses of lymphocytes to PHA, and in vivo evaluations of the cutaneous responses to five test mitogens (PPD, candidine, varidase, PHA [1 μg], and PHA [10 μg]).

Immunologic parameters tested in all of the patients in Group A deteriorated during the course of therapy. The number of OKT4 cells dropped from 7% (±8) to 1% (±1) and the number of OKT8 cells increased from 52% (±10) to 58% (±60). The OKT4:OKT8 ratio dropped from 0.15 (±0.18) to 0.03 (±0.03). The response to PHA decreased from 33,186 cpm (±34,142) to 9617 cpm (±8479). All patients were anergic before treatment and remained anergic even after therapy. Clinically, all five patients grew worse during the course of the study. All died, two from infections during the course of therapy and three within 2-8 months after therapy.

The results of immunological evaluations of the six ARC patients in Group B at various times before and during treatment are summarized in the Table. After IV bolus administration of TP5, there was a significant increase in the percent of total (OKT3) T cells, due mostly to an increase in the number of suppressor/cytotoxic (OKT8) cells. After slow infusion of additional TP5, there was significant improvement in the in vitro response to PHA over the pre-therapy value and over the post-bolus value. This was associated with an improved in vivo response: skin tests, all of which were negative before therapy, became positive in five patients after TP5 therapy. All patients also gained weight and subjective reports indicated

OLOGIC PARAMETERS IN GROUP B AIDS-RELATED COMPLEX PATIENTS
EIVING THYMOPENTIN BY TWO ROUTES OF ADMINISTRATION

	Mode of Administration			
	1 Before Treatment	2 Intravenous Bolus	3 Infusion	P*
Lymphocytes (cells/μl)	2,000 ± 1,069	2,167 ± 1,314	2,253 ± 1,575	NS
OKT3 (%)	70 ± 5	79 ± 8	73 ± 12	0.03 (1 vs. 2)
OKT4 (%)	6 ± 3	10 ± 5	7 ± 6	NS
OKT8 (%)	65 ± 8	74 ± 8	66 ± 16	0.01 (1 vs. 3)
PHA (cpm)	45,182 ± 42,300	61,311 ± 51,228	116,362 ± 75,866	0.05 (1 vs. 3) 0.02 (2 vs. 3)

All results are expressed as mean ± standard deviation. Abbreviations: cpm, counts per minute; NS, not significant; PHA, phytohemagglutinin.

* T test on paired samples.

improvement. After 8 months observation, immunological and clinical improvement persisted in four patients. One patient developed cutaneous Kaposi's sarcoma (KS) at 7 months. One patient developed opportunistic infections (OI) (Pneumocystis carinii pneumonia (PCP), esophagitis, candidiasis) and disseminated KS at 3 months. (This patient was the one showing no response to mitogens during TP5 therapy.)

The five patients in Group C showed only one common modification following TP5 therapy--a significant decrease of OKT3 cells. For one patient, subjective reports indicated improvement and weight gain was recorded. This patient developed positive skin tests, an increased OKT4:OKT8 ratio (from 0.3-0.8), and a 20-fold increase in the in vitro response to mitogens. Three patients developed OI during TP5 therapy: herpes zoster (two cases), PCP (one case), and oral candidiasis (two cases).

This preliminary study confirms a previous report (Mascart-Lemone F, Huygen K, Clumeck N: Lancet, 1983, 2: 735-736) and suggests that IV infusion with TP5 may be useful in treating patients with ARC. No effect of TP5 was noted in patients with full-blown AIDS. It is possible that in these patients the pool of lymphocytes is too seriously depleted for stimulation to occur.

The mode of administration of TP5 is important. The same dose administered in different ways can produce opposite effects (Audhya T, Goldstein G: Int J Pept Protein Res., 1983, 22:187). In addition, it has been shown in the guinea pig that, at equivalent doses, the effect of TP5 on neuromuscular transmission is higher by slow IV infusion (Ibid, p 568). In our study, 50 mg administered by slow IV infusion appears to be more effective than other doses and other routes.

This study suggests that improvement of both the clinical and the immunological status of ARC patients may be possible through high-dose TP5 therapy. Long-term double-blind studies are needed to assess whether such therapy can interfere with the natural evolution of the disease.

This paper contains information which has been accepted for presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy to be held in Washington, D.C., October 1984.

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HYPOTHESIS: THE PATHOGENESIS OF AIDS INVOLVES ACTIVATION OF T AND B CELL CASCADES

The concept advanced in this paper is that viral infection of lymphocytes can produce proliferative or lytic responses depending on the circumstances of infection. In either case, infection of lymphocytes is followed by a cascade of secondary events. AIDS may result when an agent related to the human T leukemia/lymphoma virus (HTLV) produces a lytic response in T helper cells. The sequence or cascade of events in the T cell population following lysis of T4 helper cells in AIDS would include reactivation of Epstein-Barr viruses (EBV) with production of a secondary B cell cascade, reactivation of cytomegaloviruses (CMV) and the development of Kaposi's sarcoma in genetically susceptible individuals, and perhaps reactivation of other intracellular agents. Opportunistic infections also may occur.

The T Cell Cascade. That a virus might be capable of inducing a proliferative response in T lymphocytes was first suggested by the occurrence of lymphatic tumors in non-human primates and other animals infected with herpes viruses (Deinhardt F, Deinhardt J: in Epstein MA, Achong BG (Eds): The Epstein-Barr Virus, Springer-Verlag, New York, 1979, 374-415). More recent developments associate T tropic retroviruses with various diseases of humans. For example, both virologic and antibody data indicate that a human T cell leukemia virus (HTLV-I) is present in patients with human T cell leukemia or lymphomas (Reitz MS, Jr, Kalyanaraman VS, Robert-Guroff M, et al: J Infect Dis., 1983, 147:299-305; Blattner WA, Blayney DW, Robert-Guroff M, et al: J Infect Dis., 1983, 147:406-416; Hinuma Y, Nagata K, Hanaoka M, et al: Proc Natl Acad Sci., 1981, 78:6476-6480; Miyoshi I, Kubonishi I, Yoshimoto S, et al: Nature, 1981, 294:770-771). Most recently, strong evidence has been presented which implicates [illegible] ruses (HTLV-III, IDAV, and LAV) [illegible] etiology of AIDS (Barre-Sinoussi [illegible] rmann JC, Rey F, et al: Science, 1983, 220:868-871; Popovic M, Sarngadharan MG, [illegible] E, et al: Science, 1984, 224:497-500; Gallo RC, Salahuddin SZ, Popovic M, et al: Science, 1984, 224:500-502; Schupbach J, Popovic M, Gilden RV, et al: Science, 1984, 224: 503-505; Sarngadharan MG, Popovic M, Bruch L, et al: Science, 1984, 224:506-508; Marx JL: Science, 1984, 224:475-477; Vilmer E, Barre-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). The three AIDS-associated retroviruses are probably closely related to each other, if not identical.

Immunologically, AIDS is characterized by a reversal of the helper:suppressor (T4:T8) T-cell ratio (Kornfeld H, Vande Stouwe RA, Lange M, et al: N Engl J Med., 1982, 307:729-730). Reversal of this ratio is, however, also common in asymptomatic homosexuals (Ibid) and in members of other risk groups. B lymphocytes are also affected in AIDS, with the types of alterations seen suggesting that polyclonal activation of B cells may have occurred (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458).

A virus capable of infecting T cells, especially helper T cells, could, in theory, initiate a sequence of events which could produce the various known signs and symptoms of AIDS as well as other effects. Figure 1 illustrates the steps in the hypothetical T cell cascade. The concept of a T cell cascade was originally suggested by Pagano (Pagano J: Presented at a conference on Epidemic Kaposi's Sarcoma and Opportunistic Infections in Homosexual Men, New York University, New York, March 17-19, 1983).

In theory, the infection of T4 cells by a retrovirus could initiate either a lytic response or a proliferative response (Blattner WA, Blayney DW, Robert-Guroff M, et al: J Infect Dis., 1983, 147:406-416). In the former instance, the outcome might be AIDS, while, in the latter instance, the outcome might be adult T leukemia/lymphoma (ATL). Factors which would facilitate the production of lytic effects could be different in different groups of affected individuals. These effects could be primary viral effects or secondary ones. Whatever their genesis, the lytic effects on helper T cells would impair a key link in the cell-mediated immune system. Then, impaired surveillance of malignant cells, reactivation of latent viruses, certain intracellular organisms, and other opportunistic agents, impairment of the primary immune response to these agents, and additional secondary effects could occur.

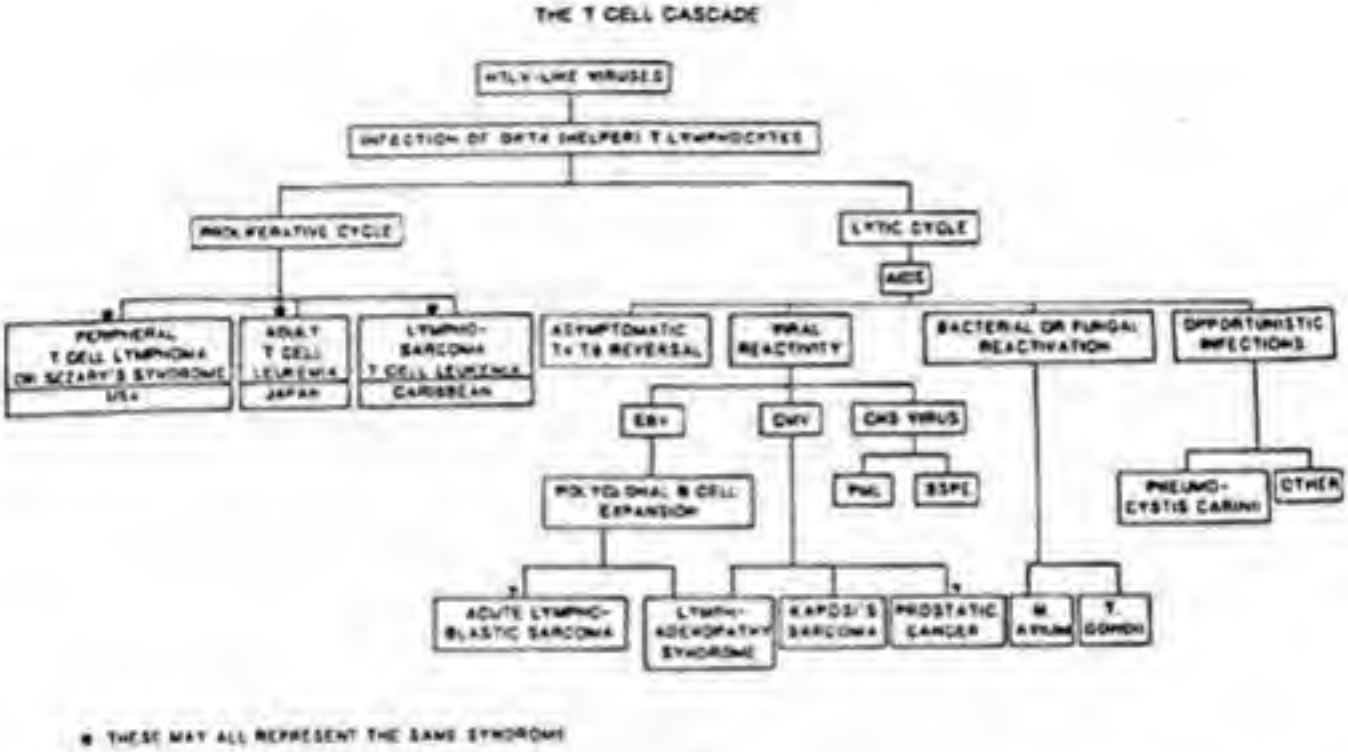

Fig. 1. Hypothetical sequence of events following infection of OKT4 (helper) T lymphocytes by a human T cell leukemia (HTLV)-like virus.

Reactivations of herpes viruses are of special interest. The reactivation of EBV in B lymphocytes can lead to polyclonal B cell proliferation (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458), the production of high titers of EBV antibody, and the various effects listed in the B cell cascade (see below). CMV reactivation might be responsible for acute CMV mononucleosis, lymphadenitis, or, in a more chronic phase, Kaposi's sarcoma (Ibid). The total possible spectrum of acute and chronic consequences of the reactivation of various latent viruses is not fully known. Additional viral effects are expected to be recognized as more persons with T4:T8 disturbances are followed for longer periods of time.

The B Cell Cascade. Activation or reactivation of EBV in infected B cells could produce several kinds of effects as indicated in the cascade presented in Figure 2. This figure is derived from various data published previously (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Evans AS: J Infect Dis., 1971, 124:330-337; Carter RL: Lancet, 1975, 1:846-855).

In the lytic cycle, anemia or hypogammaglobulinemia might result. In the proliferative cycle, transformation and

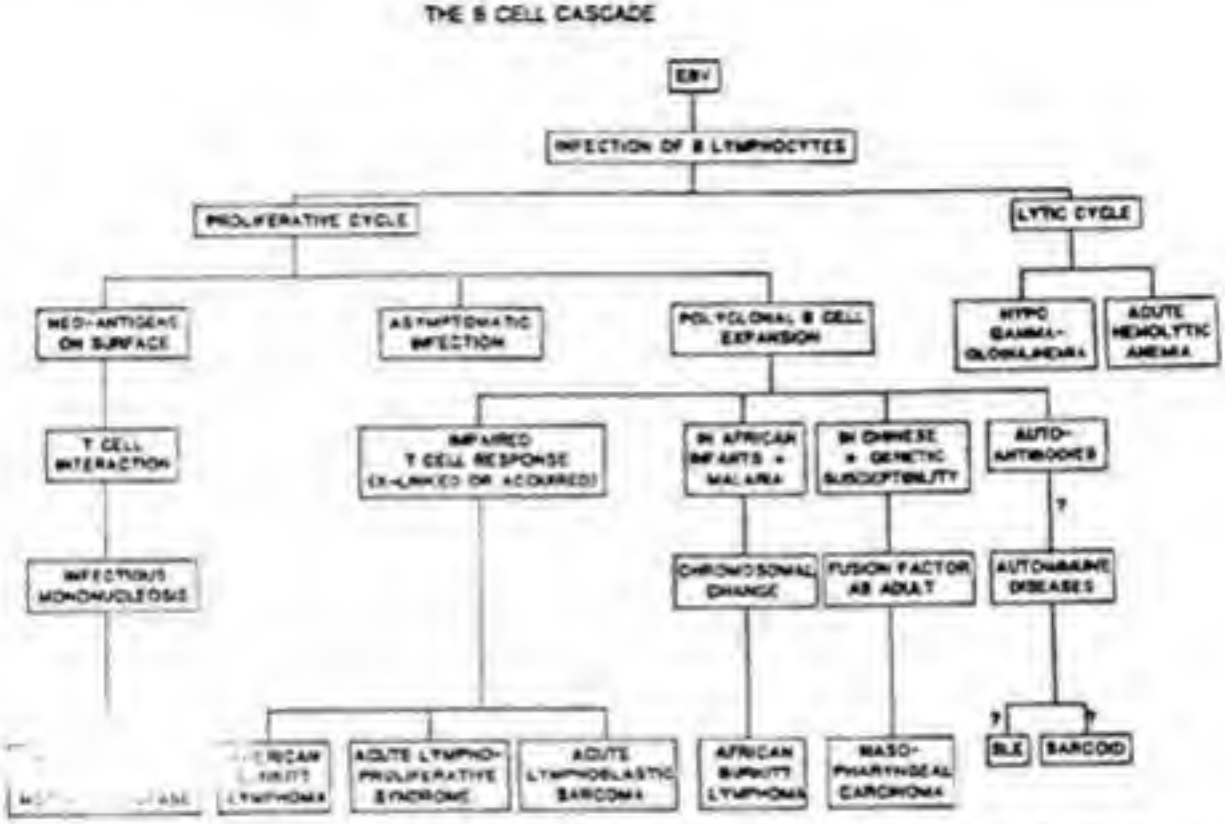

Fig. 2. Hypothetical sequence of events following infection of B lymphocytes by Epstein-Barr virus (EBV).

"immortalization" of B lymphocytes and polyclonal B cell expansion could occur. A wide spectrum of antibodies could be produced by EBV-activated B cells, including various heterophile, anti-EBV, and anti-self antibodies (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Kano K, Milgrom F: Curr Top Microbiol Immunol., 1979, 77:43-69). The induction of new antigens on the surface of EBV-infected B cells can evoke vigorous T cell responses as in infectious mononucleosis in older children and young adults. Usually this is a benign and self-limited disease in which the proliferative events are brought under control through the activities of suppressor/cytotoxic and non-specific "killer" T lymphocytes early in disease (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Thorley-Lawson DA, Chess L, Strominger JL: J Exp Med., 1977, 146:495-507; Tosato G, McGrath I, Koski I, et al: N Engl J Med., 1979, 301:1133-1137). However, when genetic (X-linked) or acquired defects in T cell responsiveness permit B cell proliferation to continue unchecked, acute lymphoblastic sarcoma may result (Purtilo DT, Hutt L, Bhawan J, et

al: Clin Immunol Immunopathol., 1978, 9:147-156; Robinson JE, Brown N, Andiman W, et al: N Engl J Med., 1980, 320:1293-1296; Snydman DR, Rudders RA, Daoust P, et al: Ann Intern Med., 1982, 96:737-742). EBV infections in Africa occurring in early infancy can lead to impaired cytotoxic and suppressor T cell responses and augmented B cell proliferation caused by holendemic malaria (de-The G, Geser A, Day NE, et al: Nature, 1978, 274:756-761). African Burkitt lymphoma can arise when chromosomal changes occur--specifically a translocation from chromosome 8 to chromosome 14--in the rapidly proliferating B cells (Miller G: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 599-619). EBV has also been associated with the development of nasopharyngeal cancer (de-The G, Ho JHC, Muir CS: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 621-652). High levels of EBV antibodies are produced in 30-40% of patients with Hodgkin's disease (Evans AS, Kirchhoff LV, Pannuti CS, et al: Am J Epidemiol., 1980, 112: 609-618; Henle W, Henle G: Int J Cancer, 1975, 16:323-328) even prior to diagnosis (Evans AS, Comstock GW: Lancet, 1981, 1:1183-1186), but viral genomes have not been demonstrated in malignant tissues (Pagano JS, Huang CH, Levine P: N Engl J Med., 1973, 289:1395-1399).

Proof that HTLV-related viruses are the etiologic agents of AIDS will involve establishment of close temporal associations between infection by the candidate agents and both clinical symptoms of AIDS and immunologic parameters. Infection with the candidate agents must precede these events and must be significantly higher in those who develop AIDS than in those who do not. Epidemiologic techniques which have been key in establishing a causal role for EBV in infectious mononucleosis (Evans AS: Presented at NIH Workshop on Epidemiology of AIDS, September 12-13, 1983; Hallee TJ, Evans AS, Neiderman JC, et al: Yale J Biol Med., 1974, 47:182-195) and in African Burkitt lymphoma (de-The G, Ho JHC, Muir CS: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 621-652) would be useful as models for establishing a causal relationship between HTLV-related viruses and AIDS.

The hypothesis presented in this paper is that an HTLV-like virus infects T4 cells causing lysis and/or suppression by T8 cells. These events initiate the reactivation of EBV, CMV, and other latent viral, bacterial, and fungal agents. Careful prospective serologic and immunological studies of susceptible persons who are at high risk are needed to associate causally the infection by candidate agents with various changes in the immune system, with changes in levels of various markers, and with the appearance of prodromal and early clinical features of AIDS.

An expanded paper including portions of this article will be published in the Yale Journal of Biology and Medicine, 1984, 57 (3).

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PREVALENCE OF KAPOSI'S SARCOMA IN AIDS PATIENTS REFLECTS DIFFERENCES IN RATES OF CYTOMEGALOVIRUS INFECTION IN HIGH RISK GROUPS

Higher morbidity due to Kaposi's sarcoma (KS) has been noted in the homosexual/bisexual AIDS risk group as compared to the heterosexual intravenous (IV) drug user risk group (DeJarlais DC, Marmor M, Thomas P, et al: N Engl J Med., 1984, 310:1119). Since several lines of evidence suggest that cytomegalovirus (CMV) may be related etiologically to KS (Giraldo G, Beth E, Henle W, et al: Int J Cancer, 1976, 22:126-131; Drew WL, Miner RC, Ziegler JL, et al: Lancet, 1982, 2:125-127), we have compared the prevalence of antibody to CMV in IV drug users with the prevalence of such antibody in homosexual men (Table).

Serum samples were collected from 94 male clients in methadone maintainence and drug detoxification programs in the San Francisco Bay area. Ninety-three percent of the subjects denied homosexual or bisexual activity. No cases of AIDS or AIDS-related complex were found. The mean duration of IV drug abuse was 10.6 years (±5.5 years SD). Ninety percent of the subjects admitted sharing needles with other drug abusers. Sixty-six percent of these subjects were seropositive for CMV antibody when evaluated by the fluorescence immunoassay (FIAX®) system of IDT, Inc. (Santa Clara, CA).

A similar study evaluating 49 patients in an out-patient drug rehabilitation program was conducted in New York City. Of the subjects in this group, 61.2% were seropositive for CMV antibody.

Previous studies have shown that 94% of homosexual men are seropositive for CMV (Drew WL, Mintz L, Miner RC, et al: J Infect Dis., 1981, 143:188-192).

These data indicate that the prevalence of CMV antibody is significantly greater in homosexual men than it is in intravenous drug abusers. The differences are statistically significant ($p < 0.001$) for both the San Francisco and New York City drug abuser groups when compared with homosexual men. If CMV contributes to the etiology of KS, the higher CMV infection rate in homosexual men may account for the greater prevalence of KS in homosexual patients with AIDS.

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POSITIVE AND NEGATIVE SEROLOGIC TESTS FOR ANTI-CYTOMEGALOVIRUS ANTIBODIES

	Intravenous Drug Users		
	San Francisco	New York	Homosexual Men
	Total = 94	Total = 49	Total = 139
CMV+	62 (66%)	30 (61.2%)	130 (94%)
CMV-	32 (34%)	19 (38.8%)	9 (6%)

AUTHOR ADDENDUM

In the AIDS Memorandum, Volume 1(5), 1984, "Reinfection with Cytomegalovirus in AIDS Patients" was contributed by W. L. Drew, E. Sweet, and E. Mocarski. Mount Zion Hospital and Medical Center, San Francisco, California 94120, and Stanford University School of Medicine, Stanford, California 94305.

AIDS IN CANADA: JULY 16, 1984

LCDC has received reports of 96 cases of AIDS in adults which comply with the case definition published by the Centers for Disease Control in Atlanta. In addition, seven cases in children have been reported but are not included in the tabulated statistics.

Age Group (years)	Male		Female		Total (% of Total)
	Alive	Dead	Alive	Dead	
Under 20	0	0	0	0	0 (0.0)
20-29	8	10	2	3	23 (23.9)
30-39	15	28	1	3	47 (49.0)
40-49	5	6	0	1	12 (12.5)
50 and over	4	9	0	1	14 (14.6)
Total (%)	32 (33.3)	53 (55.2)	3 (3.2)	8 (8.3)	96 (100.0)

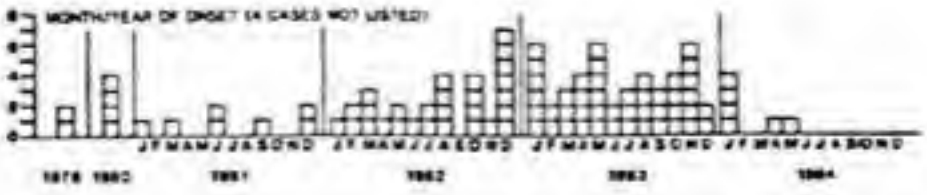
Country of Birth	Alive	Dead	Total (% of Total)
Canada	24	34	58 (60.4)
Haiti	6	20	26 (27.1)
Other	4	4	8 (8.3)
Not known	1	3	4 (4.2)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

AIDS IN CANADA

Sexual Orientation	Alive	Dead	Total (% of Total)
Homosexual/Bisexual	24	34	58 (60.4)
Heterosexual	10	22	32 (33.3)
Not Known	1	5	6 (6.3)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

Primary Disease	Alive	Dead	Total (% of Total)
[illegible]	9	11	20 (20.8)
[illegible]	16	29	45 (46.9)
Both KS and PCP	3	2	5 (5.2)
Other OI	7	19	26 (27.1)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

Abbreviations: KS, Kaposi's sarcoma; OI, opportunistic infection; PCP, Pneumocystis carinii pneumonia.



CLASSIFICATION OF CANADIAN CASES

A. Evidence of a Possible Means of Disease Acquisition	
Homosexual or bisexual practice	58
Intravenous drug abuse	1
Hemophilia	2
B. Exposure Factors	
Person of Haitian origin	24
Heterosexual partners of person(s) with AIDS or person(s) in group A	0
Recipients of blood transfusions/blood products (excluding hemophiliacs)	0
C. Children	
Infant (less than 12 months)	4
Child (1-15 years)	3
D. Person Diagnosed as Having AIDS But Not Fitting into A, B, or C Above	11

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF JULY 30, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1290	23.9	351	27.2
PCP without KS	2869	53.2	1400	48.8
Both KS and PCP	339	6.3	226	66.7
OI without KS or PCP	896	16.6	485	54.1
TOTAL	5394	100.0	2462	45.6

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infections

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homos[illegible] or bisex[illegible]	3877	77.0	0	0.0	3877	71.9
IV drug [illegible]	748	14.9	202	56.0	950	17.6
Haitian	178	3.5	30	8.3	208	3.9
Hemophiliac	41	0.8	0	0.0	41	0.8
No apparent risk group or unknown	189	3.8	129	35.7	318	5.9
TOTAL	5033	100.0	361	100.0	5394	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.